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EXAMINER	
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ART UNIT	PAPER NUMBER
[illegible]	6

DATE MAILED: [illegible]

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

See the attached.

File Copy

Office Action Summary

Application No.	Applicant(s)
08/520,946	Brow, Lyamichev And Olive
Examiner	**Group Art Unit**
William Sandals	1805

☒ Responsive to communication(s) filed on *Aug 30, 1995* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-44* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-44* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Specification

1. The disclosure is objected to because of the following informalities: In the brief description of the drawings, the description of figures 6, 20-21 and 23-24 need SEQ ID NO:'s.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claim 1 provides for the method of identifying strains of microorganisms, but, since the claim does not set forth all steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-44 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth all steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lyamichev et. al. in view of Young, Seela and Roling, and Young et. al..

The claims are drawn to a method for identifying strains of microorganisms, which may be bacteria, which may be selected from the group comprising members of the genera *Campylobacter, Escherichia, Mycobacterium, Salmonella, Shigella* and *Staphylococcus,* wherein the genus *mycobacterium* comprise strains of multi-drug resistant *Mycobacterium tuberculosis.* Also, the microorganism may be virus which may be selected from the group comprising hepatitis C virus (HCV) and simian immunodeficiency virus (SIV). The microorganisms are identified by cleaving the isolated nucleic acid of the microorganisms where the nucleic acid is treated to form (secondary) cleavage structures. The cleavage structures are cleaved with a cleavage means. The cleavage means may be an enzyme, which may be a nuclease, which may be selected from the group consisting of "Cleavase BN", *Thermos aquaticus* DNA polymerase, *Thermus thermophilus* DNA polymerase, *Escherichia coli* E.O. III, and the *Saccharomyces cerevisiae* Rad1/Rad10 complex. The nucleic acid may comprise a nucleotide analog. The nucleotide analog may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The nucleic acid may be single stranded, or RNA or DNA or may be double stranded. The double stranded nucleic

acid may be rendered single stranded. This may be done by exposing the double stranded nucleic acid to increased temperature. The cleavage products of the nucleic acid may be separated and then may be detected. The detected cleavage products may be compared with cleavage products of nucleic acid structures from reference microorganisms. The isolated nucleic acid may be a polymorphic locus which may be isolated by polymerase chain reaction (PCR). The PCR may be done with a nucleotide analog which may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The PCR primers may be matching or complementary to consensus gene sequences derived from the polymorphic locus, which may be ribosomal RNA, which may be 16S ribosomal RNA.

Lyamichev et. al. (see entire reference) taught a method for cleaving an isolated nucleic acid where the nucleic acid was treated to form (secondary) cleavage structures. The cleavage structures were cleaved with a cleavage means. The cleavage means was an enzyme, which was a nuclease, which may be selected from the group consisting of *Thermos aquatics* (Tac) DNA polymerase and *Thermos thermophilous* (Tth) DNA polymerase. The nucleic acid may be single stranded, or RNA or DNA or may be double stranded. The double stranded nucleic acid may be rendered single stranded. This may be done by exposing the double stranded nucleic acid to increased temperature. The cleavage products of the nucleic acid may be separated and then may be detected. The detected cleavage products may be compared with cleavage products of reference nucleic acid structures. The isolated nucleic acid may be a polymorphic locus which

may be isolated by polymerase chain reaction (PCR). The PCR primers may be matching or complementary to consensus gene sequences derived from the polymorphic locus.

Lyamichev et. al. did not teach a method for identifying strains of microorganisms, which may be bacteria, which may be selected from the group comprising members of the genera *Campylobacter, Escherichia, Mycobacterium, Salmonella, Shigella* and *Staphylococcus*, wherein the genus *mycobacterium* comprise strains of multi-drug resistant *Mycobacterium tuberculosis.* Lyamichev et. al. also does not teach that the microorganism may be a virus which may be selected from the group comprising hepatitis C virus and simian immunodeficiency virus. The reference does not teach that the detected cleavage products may be compared with cleavage products of nucleic acid structures from reference microorganisms. Lyamichev et. al. does not teach that the nucleic acid may comprise a nucleotide analog, where the nucleotide analog may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The reference does not teach that the PCR may be done with a nucleotide analog which may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP, or the PCR primers from ribosomal RNA, which may be 16S ribosomal RNA.

Lyamichev et. al. taught that this method can be used to optimize allele-specific PCR. The polymerase was also taught to be a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid.

Young, columns 3-4 and 10 taught the use of PCR with the nuclease *Thermos aquatics* (Tac) DNA polymerase to identify the polymorphic loci of ribosomal 16S RNA from

Mycobacterium spp. which increased the speed, accuracy and sensitivity of detection of disease causing microorganisms which were difficult to culture and could take up to several weeks to identify.

Seela and Roling, pages 55 and 61, taught the use of 7-deaza-dATP, 7-deaza-dGPT and dUTP in PCR reactions. The use of these nucleotide analogs helped protect the nucleic acids containing them from nuclease digestion, as well as reduce "read through" problems frequently encountered in polymerase reactions.

Young et. al., on page 882, taught the use of PCR with the nuclease *Thermos thermophilous* DNA polymerase for the detection of hepatitis C virus (HCV) in clinical diagnostics, which was an effective means of direct detection of HCV that streamlined the procedure, reduced potential contamination of the reaction by eliminating the addition of a second enzyme and increased specificity of the primer extension.

It would have been obvious to combine the teachings of Lyamichev et. al. with Young, Seela and Roling, and Young et. al. to produce a method for identifying strains of microorganisms, which may be bacteria, which may be selected from the group comprising members of the genera *Campylobacter, Escherichia, Mycobacterium, Salmonella, Shigella* and *Staphylococcus,* wherein the genus *mycobacterium* comprise strains of multi-drug resistant *Mycobacterium tuberculosis.* Also, the microorganism may be virus which may be selected from the group comprising hepatitis C virus and simian immunodeficiency virus. The microorganisms are identified by cleaving the isolated nucleic acid of the microorganisms where the nucleic acid is

treated to form (secondary) cleavage structures. The cleavage structures are cleaved with a cleavage means. The cleavage means may be an enzyme, which may be a nuclease, which may be selected from the group consisting of "Cleavase BN", *Thermos aquatics* DNA polymerase, *Thermos thermophilous* DNA polymerase, *Escherichia coli* E.O. III, and the *Saccharomyces cerevisiae* Rad1/Rad10 complex. The nucleic acid may comprise a nucleotide analog. The nucleotide analog may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The nucleic acid may be single stranded, or RNA or DNA or may be double stranded. The double stranded nucleic acid may be rendered single stranded. This may be done by exposing the double stranded nucleic acid to increased temperature. The cleavage products of the nucleic acid may be separated and then may be detected. The detected cleavage products may be compared with cleavage products of nucleic acid structures from reference microorganisms. The isolated nucleic acid may be a polymorphic locus which may be isolated by polymerase chain reaction (PCR). The PCR may be done with a nucleotide analog which may be selected from the group comprising 7-deaza-dATP, 7-deaza-dGTP and dUTP. The PCR primers may be matching or complementary to consensus gene sequences derived from the polymorphic locus, which may be ribosomal RNA, which may be 16S ribosomal RNA.

It would have been obvious to combine these teachings because Lyamichev et. al. taught that this method could be used to optimize allele-specific PCR. The polymerase was also taught to be a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid. Seela and Roling recited the use of Tac polymerase with nucleotide analogs 7-

deaza-dATP, 7-deaza-dGPT and dUTP in PCR reactions. The use of these nucleotide analogs would have helped protect the nucleic acids containing them from nuclease digestion, as well as reduce "read through" problems frequently encountered in polymerase reactions. Young et. al. taught the use of PCR with the nuclease *Thermos thermophilous* DNA polymerase for the detection of hepatitis C virus (HCV) in clinical diagnostics. The use of Tth DNA polymerase in PCR was an effective means of direct detection of HCV which streamlined the procedure and reduced potential contamination of the reaction by eliminating the addition of a second enzyme and increased specificity of the primer extension.

One of ordinary skill in the art would have been motivated to combine the teachings of Lyamichev et. al. with Young, Seela and Roling, and Young et. al. to produce a method that could be used to optimize allele-specific PCR wherein the polymerase is also a single stranded endonuclease which recognized hairpin structures of the single stranded nucleic acid. The method used Tth DNA polymerase or Tac DNA polymerase with nucleotide analogs 7-deaza-dATP, 7-deaza-dGPT and dUTP in PCR reactions. The use of these nucleotide analogs helped protect the nucleic acids containing them from nuclease digestion, as well as reduce "read through" problems frequently encountered in polymerase reactions. Also, the use of nuclease *Thermos thermophilous* DNA polymerase in PCR assays is an effective means of direct detection of HCV, which streamlined the procedure and reduced potential contamination of the reaction by eliminating the addition of a second enzyme and increased specificity of the primer extension.

Conclusion

4. Certain papers related to this application may be submitted to Art Unit 1805 by facsimile transmission. The FAX number is (703) 308-0294. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mindy Fleisher, can be reached at (703) 308-0407.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner

Mindy B. F

MINDY FLEISHER
SUPERVISORY PATENT EXAMINER
GROUP 1800